REMARKS

(1) The first paragraph is amended to identify the U.S patents that issued from the non-provisional patent applications identified as parent applications, as requested on page 2 of the Official Action.

(2) Lines 3, 26, 30, and 33 of claim 9 are amended to specify that the recited method involves an operation of vector or matrix algebra on input data, in response to the statement on pages 3-4 of the Official Action that the claim contains new matter. The Applicants regret any inconvenience caused the examiner by not pointing to the support for the amendment to claim 9 in the amendment filed September 25, 2000. The Applicants submit that the specification discloses multiple examples of the claimed invention, without relying on the section of page 39 that suggests applying the disclosed methods to find the product of two matrices, but does not provide a detailed description of how to do so. For example, as described on pages 29-30, addition of vectors comprises mixing single-stranded input oligomers under conditions in which complementary oligomers specifically hybridize to each other to form stable, double-stranded complexes, whereas non-complementary oligomers do not form such stable complexes, separating the stable, double-stranded complexes from the mixture of oligomers, and measuring the concentrations of the oligomers of interest remaining in the mixture. The use of hybridization conditions that are sufficiently stringent to promote specific hybridization of complementary oligomers is discussed on page 12, and the requirement that such conditions be used in carrying out vector addition is stated on lines 18-20 of page 29. As described at the bottom of page 30, multiplication of a vector by a scalar is represented by adjusting the concentration of the DNA molecules corresponding to that vector by a factor that is proportional

to the scalar; and once the concentrations of the oligomers representing the components of a vector of interest have been so adjusted, their measurement permits determination of the factor by which the vector has been multiplied. As described on pages 31-33, determination of the inner product of two vectors is based on fact that the rate of hybridization of complementary oligonucleotides in a mixture is directly proportional to the product of their concentrations in the mixture. The inner product of two vectors V and W is determined by measuring and combining two rates of hybridization - R_-, the rate with which oligomers representing components of V hybridize specifically to oligomers representing components of W, and R_+, the rate with which oligomers complementary to components of V or W hybridize specifically to oligomers representing the components of the other vector.

Obtaining a matrix representing the outer product of two vectors is described on pages 33-36, and finding the product of a matrix and a vector is described on pages 36-39. The Applicants submit that the algebraic operation of finding the outer product of two vectors to obtain a matrix may properly be classified of as an operation of matrix algebra, as well as an operation of vector algebra. As with the above-described vector operations, the result of an operation involving a matrix also depends quantitatively on the concentrations of the oligomers E_i and E_i in the composition representing the input data. A matrix representing the outer product of two vectors V and W may be obtained by joining the 3' ends of all of the oligomers representing components of V to the 5' ends of all of the oligomers representing the components of W. The result is a set of "dimeric," single-stranded oligomers, each consisting of an oligomer V_i of V joined at its 3' end to the 5' end of an oligomer W_j of W, with the concentration of each of the "dimeric" 5'-V_i -W_j -3' oligomers in the resulting set of oligomers that represents the outer product matrix being proportional to the product of the concentrations of the oligomers

representing the V_i component of V and of the oligomers representing the W_j component of W. To find the inner product of a vector X and a matrix T, the oligomers representing the positive and negative components of vector X are hybridized specifically to the oligomers that make up one "side" of the single-stranded, "dimeric," matrix oligomers, for example, the 3' side, and the inner product is obtained by collecting the oligomers of the other side, e.g., the 5' side, of the matrix oligomers from the complexes formed by hybridization with the oligomers representing the components of vector X. The concentrations of oligomers collected as the inner product of vector X and a matrix T are proportional to the rate of hybridization of the oligomers representing the components of vector X with their complements in the dimeric matrix T oligomers; accordingly, and so are dependent on the concentrations of the oligomers representing the positive and negative components of vector X in the composition representing the input data.

In summary, the specification provides at least two examples each of operations of vector and matrix algebra, the results of which depend quantitatively on the concentrations of the single-stranded oligomers E_i and E_i in the composition representing input data, in support of the amended claim. The Applicants respectfully submit that the amended claim does not contain new matter.

(3) Claim 11 is amended to specify phosphorylating or de-phosphorylating the 5' terminus of an oligomer, in response to the statement on pages 2-3 of the Official Action that the claim contains new matter. Phosphorylation and de-phosphorylation of the 5' terminus of an oligomer are described in the specification in the following paragraph that bridging pages 33-34:

> "(I) To ensure that the V_i and W_j strands are attached to each other in the proper orientation, the 5'

phosphate residues are removed from the V_i oligomers, e.g., using bacterial alkaline phosphatase, and the 5' termini of the W_j are phosphorylated, e.g., using bacteriophage T4 polynucleotide kinase."

The claim has been amended in recognition that the claim currently encompasses modifying either the 5' or 3' terminus, but the specification describes phosphorylating or de-phosphorylating only the 5' terminus. The specification clearly suggests phosphorylating or de-phosphorylating the 5' terminus by using the specific enzymes bacteriophage T4 polynucleotide kinase and bacterial alkaline phosphatase by way of example, as indicated by the abbreviation "e.g." that precedes each of the enzyme names in lines 1 and 3 on page 34. At the time the invention was made, one skilled in the art would also have known of other common methods for phosphorylating or de-phosphorylating the 5' terminus of an oligomer in an enzyme-catalyzed reaction. For example, one skilled in the art would have known that the 5' terminus could also be phosphorylated using polydeoxyribonucleotide kinases isolated from calf thymus or rat liver (see Karimi-Busheri et al., J. Cell Biochem. 64(2):258-272, 1997, and Prinos et al., J. Cell Biochem., 58(1)115-131, 1995), and that it could also be de-phosphorylated using Calf Intestinal Alkaline Phosphatase (see BioLabs 1994 catalog, page 75), or thermolabile alkaline phosphatase from the bacteria HK-47 (See U.S. Patent No. 4,720,458). The Applicants submit the requirement to remove new matter in claim 11 is met by amending the claim to specify that the phosphorylating or de-phosphorylating activity is directed at the 5' terminus. The Applicants respectfully submit, in addition, that claim 11 should not be limited to a method that uses the particular enzymes - bacteriophage T4 polynucleotide kinase and bacterial alkaline phosphatase - that are disclosed in the specification for carrying out the recited reactions, since those skilled in

the art at the time of the invention would have recognized that the specific kinase or phosphatase enzyme that is used to modify the 5' ends of the oligomers is not an essential feature of the invention, and, as discussed above, would have known of other kinase and phosphatase enzymes with essentially the same activities as the enzymes suggested in the specification that would also be expected to operate successfully in the claimed invention. In support of its statement that new matter is impermissible, the Official Action cites In re Winkhaus, Tusche, and Kampf, 188 USPQ 129 (CCPA 1975), which stated that in accord with the prohibition of new matter stated in 35 U.S.C. § 132, a method claim may not be amended to recite a step that is not disclosed by the specification as filed, even if one skilled in the art would have been expected to consider that the recited step was possible. See id., pages 130-131. The Applicants submit that the Winkhaus decision is not applicable in the present context, because the amended claim does not include any steps that are not expressly disclosed in the specification.

(4) Section (c) of claim 17 is amended in response to the statement on pages 4-5 of the Official Action that recitation that "the number of X_i oligomers for at least one basis vector e_i is greater than the number of E_i or $\underline{E}_i$ saturating oligomers corresponding to said basis vector" constitutes new matter. The objected-to phrase of section (c) of claim 17 has been amended to recite that "the number of oligomers in the set of X_i oligomers is greater than the number of saturating oligomers." Support for the amendment is found at page 48, lines 18-20, and page 49, lines 14-16, which state that the tethered saturating oligomers are sub-stoichiometric with respect to the X_i oligomers. The Applicants respectfully submit that the amended claim does not contain new matter.

(5) Claim 27 is amended in response to the statement on pages 4-5 of the Official Action that recitation that,

> "oligomers that represent components of said vectors $\boldsymbol{V}$, $\boldsymbol{W}$, and $\underline{\boldsymbol{W}}$ having different basis vectors do not hybridize under conditions in which complementary oligomers E_i and $\underline{E}_i$ corresponding to the same basis vector $\boldsymbol{e}_i$ do hybridize"

constitutes new matter. In the amended claims, the objected-to statement is replaced with the recitation that,

> "the nucleotide sequences of oligomers that represent the components of said vectors $\boldsymbol{V}$, $\boldsymbol{W}$, and $\underline{\boldsymbol{W}}$ have minimal overlap with the nucleotide sequences of the oligomers representing the other components of said vectors."

Similarly, claim 28 is amended by replacing the analogous statement with the recitation that,

> "the nucleotide sequences of oligomers that represent the components of said matrix $\mathbf{T}$ and said vector $\mathbf{V}$ have minimal overlap with the nucleotide sequences of the oligomers representing the other components of said matrix and said vector."

Support for these amendments is found at page 28, lines 7-12, and page 29, lines 9-12, of the specification. The condition of selecting the oligomers representing vector components to have minimal sequence overlap is actually taught as being a general feature of the invention in all of its embodiments, and its reiteration in claims 27 and 28 may be regarded as being something of a redundancy; however, the condition is nonetheless expressed in these claims

to allow the claimed methods to be understood with the greatest clarity. The Applicants respectfully submit that the amended claims do not contain new matter.

(6) Claim 13 is amended to include the recitation of the limitation that the oligomers in the mixture are allowed to hybridize

> "under conditions that allow only complementary E_i and $\underline{E}_i$ strands to hybridize to form stable double-stranded DNA complexes."

The Applicants respectfully submit that the scope of the amended claim is commensurate with the support provided by the description of the invention in the specification, in compliance with the first paragraph of 35 USC § 112.

(7) As noted above, claim 27 is amended to include the recitation that,

> "the nucleotide sequences of oligomers that represent the components of said vectors ***V***, ***W***, and ***$\underline{W}$*** have minimal overlap with the nucleotide sequences of the oligomers representing the other components of said vectors;"

and claim 28 is amended to state that,

> "the nucleotide sequences of oligomers that represent the components of said matrix **T** and said vector **V** have minimal overlap with the nucleotide sequences of the oligomers representing the other components of said matrix and said vector."

In providing guidance for selecting the nucleotide sequences associated with the basis vectors $\mathbf{e}_i$ of the vectors and matrices of the disclosed invention, the specification (p. 28, lines 7-12) teaches that,

> "[t]o prevent introduction of error into the operations by undesired interactions between DNA oligomers which are not fully complementary, the nucleotide sequences of the DNA n-mers are preferably selected so that the DNA n-mers are non-palindromic, relatively free of hairpin effects, and have minimal overlap with the other basis vectors."

Those skilled in the art would understand that the avoiding of sequence "overlap" in this context refers to avoiding selecting nucleotide sequences to represent different basis vectors that have undesired regions of sequence complementarity that would result in undesired hybridizations during the practice of the claimed invention. Along the same line, those skilled in the art would readily comprehend that optimal hybridization conditions for practicing the claimed invention would typically be conditions under which complementary oligomers hybridize specifically with each other (and not to other oligomers), as discussed on page 12, lines 5-15, and would have little difficulty in using routine methods to identify such favorable hybridization conditions. Applicants submit that the claims must be interpreted in light of the specification as a whole, and in particular, in light of these basic teachings about the methods disclosed in the specification. Given the teaching in the specification of the importance of selecting oligomers with minimal sequence overlap, and the general teaching that in order to be successful, the hybridization reactions of the disclosed methods must typically be carried out in a manner that would distinguish and/or separate complementary oligomers from non-

complementary ones, one skilled in the art would recognize that the material added to claims 27 and 28 is inherent, and would practice the claimed inventions accordingly. Accordingly, the Applicants respectfully submit that the scope of amended claims 27 and 28 is commensurate with the support provided by the description of the invention in the specification, in compliance with the first paragraph of 35 USC § 112. Following the teachings of the specification, one skilled in the art would be able to practice the claimed methods successfully with all possible vectors, and not just orthogonal ones.

(8) Claim 15 is amended to recite that the dimeric, single-stranded matrix oligomers each comprise a first oligomer sequence that is joined at its 3' end to the 5' end of a second oligomer sequence. Applicants respectfully submit that one skilled in the art would be able to follow the teachings of the claimed invention to practice the method of amended claim 15.

(9) As noted above, section (c) of claim 17 is amended to show that the phrase "wherein the E_i and E_i oligomers are sub-stoichiometric relative to said set of X_i oligomers, connotes that "the number of oligomers in the set of X_i oligomers is greater than the number of saturating oligomers." Applicants submit that one skilled in the art would clearly understand the meaning of amended claim 17.

(10) Claim 25 is amended to recite that,

"each dimeric oligomer in the set of oligomers for each vector $\mathbf{V}^a$ comprises a first single-stranded oligomer sequence selected from the group consisting

of E_i or $\underline{E}_i$ for each i-th component of $\mathbf{v}^a$ for i = 1, 2, ...m,

which oligomer is attached at its 3′ end to the 5′ end of a second single-stranded oligomer sequence selected from the group consisting of E_j or $\underline{E}_j$ for each j-th component of $\mathbf{v}^a$ for all j = 1 to j = m, except for i = j."

Applicants respectfully submit amended claim 25 clearly describes to one skilled in the art what is meant by reference to a "dimeric" matrix oligomer.

(11) Applicant respectfully submits that claims 9-11 are clearly distinct from, and are not anticipated by, the methods of Adleman, Guarlieri, or Oliver, since none of the prior art methods disclose methods for which the result of the vector or matrix algebra operation is quantitatively dependent on the concentration of the input oligomers.

(12) Applicant respectfully submits that claims 26 and 26 are clearly distinct from, and are not anticipated by, the compositions disclosed by Southern, since none of the prior art compositions are a set of dimeric oligomers as disclosed in claims 25 and 26.

Respectfully submitted,

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